

Application No. 10/537,280  
Amendment Dated: September 14, 2009  
Response to Office Action mailed June 2, 2009

#### REMARKS/ARGUMENTS

This amendment is filed in response to the Office Action mailed June 2, 2009 for the above captioned application. Reconsideration of the application as amended in view of the remarks herein is respectfully requested.

Applicants apologize for the inadvertent mislabeling of claim 168, and have corrected the status indicator to withdrawn in this amendment.

In the present amendment, changes are made to claims 200 and 202 in view of the comments in the final office action. Since the rejections to which these amendments respond were presented in that office action, the responsive amendment could not have been made sooner. Further, it is believed that the amendments as discussed below overcome the rejections. Thus, entry of these amendments after final is appropriate.

Claims 121 and 122 stand rejected under 35 USC § 102 as anticipated by WO 91/09137. The Examiner argues that the '137 application discloses monoclonal antibodies within the scope of the claims, because the polyclonal sera disclosed "are comprised of a multiplicity of monoclonal antibodies each directed to specific antigenic epitopes." (Office Action Page 3) . This argument is wholly inconsistent with the meaning of the ordinary meaning of the term "monoclonal" as it is used in the art.

Applicants disagree with the Examiner's characterization of polyclonal serum as a mixture of monoclonal antibodies. Such polyclonal serum is a mixture that contains many antibodies. Some of them are for the particular antigen to which they were raised, and others are simply endogenous antibodies to other antigens. Because each of the antibodies are in a mixture with antibodies to other antigens, and antibodies originating from different B cells, none of them can be considered a "monoclonal antibody" which in accordance with the art, requires that only antibodies from a single clonal source be present.

Monoclonal antibodies are populations of antibodies in which all of the antibodies are identical because they are derived from clones of a single parent cell. (Ex. A) Polyclonal antibodies on the other hand are, as the name indicates, populations of antibodies that are derived from clones of more than one parent cells. (Exs. B-D) Thus, monoclonal antibodies are different from polyclonal antibodies. Indeed, Ex. D states that the term "polyclonal antibody" is used "to describe whole serum raised against a particular antibody **to distinguish it from a monoclonal antibody.**" A polyclonal mixture of antibodies is not a monoclonal antibody, and is certainly not an isolated or purified monoclonal antibody as claimed. Therefore, there is plainly no anticipation, and the rejection of claims 121 and 122 should be withdrawn.

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Claims 121, 122, 126, 127, 130, 133, 136, 137 and 198 stand rejected as obvious over the '137 application and van der Heijden with additional references considered as evidence. Applicants submit that this rejection is founded on mischaracterizations of the references and wholly unsupported allegations, and that it fails to present a *prima facie* case of obviousness.

The starting point of this rejection appears to be the rejection under § 102 which, as discussed above, is in error. A polyclonal serum is not a mixture of monoclonal antibodies, and the statement is in fact an oxymoron, since if multiple species of monoclonal antibodies were mixed together they would cease to be monoclonal. Furthermore, while the Examiner identifies at Page 5, ¶ (a) characteristics of the polyclonal sera of the '137 application, and links this to the statements of functional characteristics in claims 121 and 122, these characteristics **are properties of the polyclonal mixture**, and are not attributed to any **one** antibody within the mixture. Thus, the complex polyclonal mixture is not an isolated or purified monoclonal antibody as claimed.

Because of this error, ¶ (b) of the statement of facts is incomplete. The '137 application does not teach **any** human monoclonal antibodies with the requisite characteristics. Nor does it teach any fragments of such monoclonal antibodies, which the Examiner acknowledges.

Based on the foregoing, a valid question that the examiner should be addressing (but is not) is whether it would have been obvious to a person skilled in the art that a monoclonal antibody with the characteristics listed in claims 121 and 122 even could be made. Nothing in the '137 patent indicates that such an antibody exists. A polyclonal mixture may contain a first antibody that performs a first function, and a second and different antibody that performs a second and different function. A mixture of these antibodies will be observed to perform both functions, and this is all that the '137 application reports. Nothing requires that there be a single antibody that performs both functions.

Moreover, other art of record supports that the idea that the functions reported in the '137 application are provided by different antibodies. In the Akamizu paper previously cited, two monoclonal antibodies were described but neither had both of the recited functions. (Previously filed 132 Declaration, ¶ 7). Similarly, while the Kohn paper disclosed monoclonal antibodies with one of the properties, none is disclosed with both the properties required in the present claims. (132 declaration, ¶¶ 8 - 10). Given the failure of these authors to identify a monoclonal antibody within the scope of the present claims (a fact acknowledged when the rejections bases on these references were withdrawn), there is no apparent reasons why a person skilled in the art would have any expectation that such a monoclonal antibody could exist.

The additional art now cited in combination with the '137 application does not alter this conclusion. As characterized by the Examiner, van der Heijden teaches fragments of human

monoclonal antibodies. The Examiner does not argue, however, that any of the monoclonal antibodies from which these fragments are derived meet the limitations of claims 121 or 122.

With respect to ¶(c), knowledge of the linear sequence of human TSHR (UniProt) does not contribute to any understanding of the three dimensional structure and whether or not there is one epitope associated with both of the functions recited in claims 121 and 122.

With respect to ¶ (d), the basic procedures to produce hybridomas is indeed routine if extensive. However, that does not lead a person skilled in the art to expect to be able to obtain a monoclonal antibody with the properties as recited in claim 121 or 122.

With respect to ¶ (f), Kohn does indeed test the properties as recited in claims 121 and 122. Kohn also did not find any monoclonal antibodies with both functions.

With respect to ¶ (g), the Examiner has overgeneralized the teaching of Saper et al. Saper teaches that one specific situation, immunohistochemistry where there is actually only one epitope on the target, and hence only one type of antibody targeting that epitope, that the polyclonal serum, with all its other antibodies, can function as a monoclonal antibody. It does not support a generalization that this is true in any other circumstance. Further, as discussed above, the unsupported statement that “polyclonal sera are comprised of a multiplicity of **monoclonal** antibodies” is simply wrong.

¶¶ (h) and (i) are irrelevant because while as a general matter it might be known how to make and purify fragments of monoclonal or recombinant antibodies, you have to start with a monoclonal or recombinant antibody. Here, that starting point is not in the art and is not obvious from the art.

In ¶ (k), the Examiner argues, without supporting evidence that “there were a finite number of predictable potential solutions recognized in the art to solve the problem” which he states in ¶ (j) is defined in the ‘137 application. This statement is made without any support as to the number of solutions (i.e. why they should be considered finite), and why they would have been predictable. Moreover, even if there were some predictable solutions, Applicants submit that the presently claimed solution is not one of them because it was unpredictable that a monoclonal antibody with the properties recited in the claims could be made, since none of the antibodies described in the art are shown to have these properties.

¶ (l) states merely a generalization one would expect to get some monoclonal antibody using the known techniques. It says nothing about an expectation of success in arriving at a monoclonal antibody with the properties recited in the present claims. Moreover, at the time of the present invention, and based on the failure of others to obtain such antibodies, those skilled in

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the art doubted that antibodies with both of the characteristics required by the present claims would even exist. See Costagliola et al, attached to the amendment filed June 30, 2008, Ex. D, Page 1039, right hand column). Costagliola is written by a third party skilled in the art acknowledging that the monoclonal antibodies as claimed were not predictable. Applicants now attach the "Talking Points" section of the issue of the Lancet and in which applicants' disclosure of the present invention was published and a third party commentary on its potential. Both of these provide clear evidence that the invention was not one that was obvious in the art.

For all of the foregoing reasons, Applicants submit that the presently claimed invention is not obvious over the cited art. Withdrawal of the § 103 rejection is therefore urged.

Claims 200-203 were rejected under § 101 as drawn to a product of nature. Independent Claims 200 and 202 have been amended in accordance with the examiner's suggestion to recite "isolated and/or purified."

Claim 202 was rejected as anticipated by US 5,565,332. Claim 202 has been amended to recite that the antibody binds to TSH-receptor. Since the partial sequence cited is from a structure that binds TNF, this should fully overcome the rejection, and is consistent with the scope of claim 203, which recites VL or VL CDRs associated with TSH-receptor binding, thus raising no new issues.

Finally, the Examiner has provisionally rejected 121, 122, 126, 127, 129, 130, 133, 136, 137 and 198 for obviousness-type double patenting in view of application No. 12/333,741. Applicants believe the Examiner intended to refer to application no. 12/333,714. Without conceding the merits of the provisional rejection, since Applicants believe that this is the only rejection which could be continued in this case, Applicants submit that maintaining it would be inconsistent with MPEP § 804 (B) (The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application **unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications.**)

It is further noted that the Examiner includes a provisional rejection of claims not in this application over Application No. 11/775,189, now abandoned, which has nothing to do with the present application. This is believed to be a word processing carry over and therefore is not addressed further.

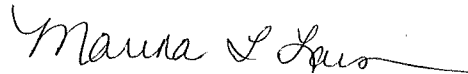
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For the foregoing reasons, Applicants submit that this application is now in form for allowance. Should there be minor matters which might be resolved by telephone to achieve allowance, the Examiner is encouraged to call the undersigned.

Respectfully submitted,

A handwritten signature in cursive script, reading "Marina T. Larson", followed by a horizontal line.

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